REMARKS

Claims 3-21 are pending in the instant application. Claims 4, 7, 9, 10, 13, 18, and 19 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 3, 5, 6, 8, 11, 12, 14-17, 20, and 21 are currently being examined on the merits. Applicants thank the Examiner for re-opening prosecution of the instant application.

Applicants also respectfully remind the Examiner that claims 4, 7, 9, 10, 13, 18 and 19 are "method of making" and "method of use" claims which all ultimately depend from product claim 3. Therefore, upon allowance of claim 3, it is believed that claims 4, 7, 9, 10, 13, 18 and 19 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)."

Claim 3 has been amended to further clarify the intended subject matter of the claimed invention. No new matter is added by this amendment. Entry of this amendment is respectfully requested.

Utility rejections under 35 U.S.C. §§ 101 and 112, first paragraph

The rejection of claims 3, 5, 6, 8, 11, 12, 14-17, 20, and 21 under 35 U.S.C. §§ 101 and 112, first paragraph for alleged lack of utility was maintained. The Office Action asserts that the claimed invention lacks a credible asserted utility or a well-established utility (Office Action, page 3). **The rejection of claims 3, 5, 6, 8, 11, 12, 14-17, 20, and 21 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.**

The invention at issue is identified in the patent application as an antibody that specifically binds to growth-associated protease inhibitor heavy chain precursor (GAPIP), which is a polypeptide encoded by a gene that is expressed in reproductive, gastrointestinal, nervous, and fetal tissues of humans (specification, page 15, lines 10-11). The novel polypeptide GAPIP to which the claimed antibody specifically binds is demonstrated in the specification to be a member of the protease inhibitor family (specification, pages 14-15), whose biological functions include regulation of the activity and

effect of proteases, and control of pathogenesis in proteolytic disorders and in treatment of HIV (specification, page 2, lines 21-23). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the polypeptide to which the claimed antibody specifically binds is a member of the protease inhibitor family alone demonstrates utility beyond the reasonable probability required by law. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds also have patentable utility, regardless of their actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. The Declaration of Lars Michael Furness (previously submitted with the Office Response of November 18, 2002) described some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration described, in particular, how the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate (Furness Declaration at ¶ 10).

The Patent Examiner does not dispute that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

As demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in the absence of any knowledge as to the precise function of the protein. The uses of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

A. Uses of the Claimed Antibodies Were Well-Established Prior To Applicants' Filing Date

The Office Action asserts that the asserted utilities for the claimed antibodies in toxicology testing are "not considered substantial and credible" (Final Office Action, page 5).

In response, Applicants file herewith the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, together with Exhibits A - Q. These submissions establish that, prior to the filing date of the instant application, it was well-established in the art that:

> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types (Rockett Declaration, ¶ 15);
>
> expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts (Rockett Declaration, ¶ 11);
>
> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments (Rockett Declaration, ¶¶ 10, 14);
>
> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal (Tab M, page 60, col. 1);
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and

thus more useful expression pattern in such analyses than would otherwise have been possible (Rockett Declaration, ¶¶ 10, 14, 17);

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool (Rockett Declaration, ¶¶ 10, 14); and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool (Rockett Declaration, ¶¶ 10, 14).

While Dr. Rockett's Declaration discusses both gene and protein expression profiling applications, the Declaration makes clear that "[i]t is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state" (Rockett Declaration, ¶ 11).

In particular, Dr. Rockett states that "[t]he principles in paragraph 10 also apply to protein expression profiling analyses, particularly to analyses performed using antibody microarrays. Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s" (Rockett Declaration, ¶ 14).

As Dr. Rockett attests, "antibody microarrays date back to the work of Roger Ekins in the mid- to late-1980s" (Rockett Declaration, ¶ 13). References describing the development of the multianalyte microspot immunoassay are attached as Tabs M-Q.

In his paper published in 1989 (attached as Tab M), over five years before the priority date of the instant application, Ekins describes his multi-analyte immunoassay systems as being useful to simultaneously measure virtually any number of individual analytes from selected analyte 'menus' (e.g. a hormone menu, viral antigen menu, an allergen menu, etc) (Tab M, page 69, col. 1). Ekins concludes that "[s]ystems capable of measuring every hormone and other endocrinologically related substance within a single small sample of blood are within reach, providing data which, when analysed with the aid of computer-based 'expert' pattern-recognition systems, are likely to reveal endocrine deficiencies only

dimly perceived using current 'single analyte' diagnostic procedures" (Tab M, page 77, col. 1).

Note that this technique does not require knowledge of the precise biological functions of the proteins to be detected, as they are described only as members of very broad categories such as viral antigens, allergens, or endocrinologically related proteins. One of skill in the art would understand that if it was valuable to analyze the expression patterns of all proteins associated with the endocrine system in order to provide more sensitive detection of endocrine disorders, it would be equally valuable to analyze the expression patterns of proteins associated with the regulation of protease activity, particularly a well defined family such as the inter-α-trypsin inhibitors, in order to provide more sensitive detection of proteolytic disorders, including reproductive, developmental, neoplastic, and immunological disorders associated with protease regulation.

Accordingly, Dr. Rockett concludes that: "It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology"[1] (Rockett Declaration, ¶ 18).

B. The similarity of the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to another of undisputed utility demonstrates utility

Because there is a substantial likelihood that the claimed GAPIP is functionally related to human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3, polypeptides of undisputed utility, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. See *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds shares more than 40 % sequence identity

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[1] Declaration of John C. Rockett, ¶ 18. "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

over 70 amino acid residues with human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3. For example, over the 70 amino acid residues from G271 to I340 of SEQ ID NO:1, SEQ ID NO:1 has 55%, 48% and 54% amino acid sequence identity to human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3, respectively: This is more than enough homology to demonstrate a reasonable probability that the utility of human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 1, enclosed). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 is, accordingly, very high.

The Patent Office must accept the Applicants' demonstration that the homology between the claimed invention and human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 demonstrates utility by a reasonable probability unless the Patent Office can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Office Action cites literature identifying some of the difficulties that may be involved in predicting protein function, none suggest that functional homology cannot be inferred by a reasonable probability in this case. Importantly, none contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. Nor do they contradict the presence of a conserved protein interaction domain, vWFA3, characteristic of protease inhibitors. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

1. Sequence homology and prediction of protein function

The Office Action acknowledges the homology of GAPIP to known members of the inter-α-trypsin inhibitor family, but asserts that "there is no clear guidance from the specification that the protein would have the same or similar biological properties as human pre-inter-α-trypsin inhibitor because the proposed uses for the claimed computer deduced protein are based solely upon computer alignment with known proteins" (Office Action, page 4).

The Office Action offers no scientific evidence in support of this assertion, although the Office Action mailed March 11, 2003, did cite Skolnick et al. as demonstrating that knowing the protein structure by itself is insufficient to annotate a number of functional classes. However, Skolnick et al. disclose that there are only 30-50% of proteins whose function cannot be assigned by any current methods (Skolnick, page 37, col. 2). This makes it more likely than not that the claimed polypeptides, which are homologous to members of a known and well characterized functional family, the inter-α-trypsin inhibitor heavy chains, are among the group which can be properly annotated.

Furthermore, Skolnick et al. state that what is really needed to predict the multifunctional aspects of proteins is "a method specifically to recognize active sites and binding regions in these protein structures" (Skolnick, page 35, col. 1). The specification discloses that GAPIP contains a vWFA3 domain, which includes the potential metal-binding site G-X-S-X-S, from N295 to N440 (specification, page 14, lines 26-28). The specification further discloses that the vWFA3 motif is a known protein-protein interaction site that is characteristic of protease inhibitors (specification, page 2, lines 12-15). Thus the functional family to which GAPIP belongs has been confirmed by more than one analytical technique.

The Examiner's attention is also respectfully directed to the enclosed reference which analyses the relationship between protein structure or sequence and protein function for single domain enzymes (Hedi Hegyi and Mark Gerstein, The relationship between protein structure and function: a comprehensive survey with application to the yeast genome, J. Mol. Biol. 288:147-164 (1999) Reference No. 2). The Hegyi paper discloses that "the proportion of homologues with different functions is around 10%. This shows that **there is a low chance that a single-domain protein, highly homologous to a known enzyme, has a different function**" (Hegyi, page 159, col. 1, emphasis added). Note also that Table 4, showing those domains having more than one function, does

not include any domains associated with any family of protease inhibitors. Thus one of ordinary skill in the art would understand that it is far more likely than not (at least 90%) that GAPIP is an inter-α-trypsin inhibitor heavy chain.

Furthermore, postfiling art **confirms** that GAPIP is a an inter-α-trypsin inhibitor heavy chain. The attached reference (Himmelfarb, M. et al., "ITIH5, a novel member of the inter-α-trypsin inhibitor heavy chain family is downregulated in breast cancer," Cancer Lett. 204:69-77 (2004) (Reference No. 3, enclosed) discloses a novel inter-α-trypsin heavy chain protein, ITIH5. As shown in the attached sequence alignment (Exhibit A), SEQ ID NO:1 has 99% identity to ITIH5, with only one amino acid substitution over the 942 amino acid length of both proteins. ITIH5 was identified "based on protein alignments as well as the existence of characteristic domains and a conserved cleavage site" (Himmelfarb, page 76, col. 2). The conserved domains include the vWFA domain identified in the specification (page 14, lines 26-28). The results of the Himmelfarb paper support the methods used by Applicants to identify protein function, and demonstrates that they are accepted in the art.

The paper also confirms that SEQ ID NO:1 is in fact an **expressed protein**, not a "putative protein product" as asserted in the Office Action (page 3). The Himmelfarb paper also demonstrated "a significant downregulation of ITIH5 in breast tumors" showing more than two-fold downregulation in eight of nine analysed normal/tumor pairs (Himmelfarb, page 76, col. 2). The authors note that "[w]hile normal breast epithelial cells clearly express ITIH5, expression is consistantly lost or downregulated in invasive ductal carcinoma" (Himmelfarb, page 69, Abstract). The authors suggest that ITIH5 has a role in breast tumorigenesis, with the loss of ITIH5 facilitating the progression to a more invasive tumor phenotype (Himmelfarb, page 76, col. 2). Thus the Himmelfarb paper confirms not only that GAPIP/ITIH5 is an expressed human protein, and that it is an inter-α-trypsin inhibitor heavy chain, but that its expression is correlated with neoplastic disorders such as breast cancer.

2. The Office Action's misapplication and distortion of the teachings of Brenner et al. regarding the reliability of sequence identity in predicting functional similarity

The Office Action also misinterprets the teachings of Brenner et al. Brenner et al. discuss the reliability of assignment of structural and functional relationship between known sequences and homologous ones, such as Applicants' assignment of the relationship between the known human inter-

a-typsin inhibitors pre-inter-α-trypsin inhibitor, pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3, and the polypeptide bound by the claimed antibodies which has 55%, 48% and 54% amino acid sequence identity, respectively, to each of these proteins over the 70 amino acid residues from G271 to I340 of SEQ ID NO:1. Through exhaustive analysis of a dataset of proteins with known structural and functional relationships, Brenner et al. have determined that 40% identity is a reliable threshold when aligned over at least 70 residues (Brenner, pages 6073 and 6076). This evidence should have been more than sufficient to end the discussion of the credibility, to the degree required by 35 U.S.C. §§ 101 and 112, first paragraph, of Applicants' assignment of function to the claimed polypeptide.

The Office Action cites caveats in Brenner et al. which discuss how such results might be skewed (**not** rendered unreliable) by the selection of sequences in the database. This clearly does not undermine the conclusions of the paper at all. The Office Action further cites Brenner's discussion of other useful information relating to structure which can be used to supplement (**not** to replace) the sequences comparisons, and then misconstrues the clear meaning of Brenner's statement that "comparing structures is a more powerful (if less convenient) way to recognize distant evolutionary relationships than comparing sequences" to imply that there is something improper or unreliable about comparing sequences. This is a plainly incorrect interpretation of Brenner's statement. Brenner's statement clearly points to the fact that sequence comparisons are **limited** in their ability to identify some distant relationships that can be better seen using structural comparisons – the clear conclusion being that sequence comparisons **under-identify** (and thus miss) actual structure/function relationships rather than misidentify them. In fact, the Office Action completely ignores the quote taken from the Abstract of the paper that sums up the teaching of this reference: "**Because many homologs have low sequence similarity, most distant relationships cannot be detected by any pairwise comparison method; however *those which are identified may be used with confidence*".** (Emphasis added.) Nothing the Office Action asserts addresses this fundamental teaching of this reference. Clearly, the 48-55% sequence identity between the known human inter-α-trypsin inhibitors and the claimed novel human inter-α-trypsin inhibitor GAPIP is a credible basis for Applicants' assertion of utility.

3. The Patent Office has not met its burden of making a *prima facie* case for lack of utility

The Office Actions's factual and scientific arguments are neither adequately supported nor do they rise to the level of adequacy necessary to overcome the presumption of objective truth of Applicants' assertions of utility and enablement.

Applicants first reiterate their primary position, which is that the Patent Office has failed in the first place to establish a proper *prima facie* case of lack of utility or enablement sufficient to shift the burden to Applicants to overcome, and that therefore, no rebuttal of this rejection should ever have been necessary. The Office Action's mere expression of doubt regarding the reliability of homology-based assignment of function (and thus use) is insufficient to support the necessary conclusion that one of ordinary skill in the art, reading Applicants' specification and claims, together with any evidence or sound scientific reasoning supplied by the Office Action, would doubt the veracity of Applicants' asserted use, i.e., that the skilled worker would find it more likely than not that the asserted utility and enabling disclosure was wrong and inoperable. It is only if that initial burden belonging to the Patent Office is met that the burden of proof of utility and enablement shifts to the Applicants.

In any case, the evidence proffered to support the contention that the skilled worker would doubt the veracity of Applicants' asserted use(s) is inadequate to meet this initial burden, as discussed above.

In addition, it is noted that, according to recent conversations with supervisory personnel in Technology Center 1600 of the USPTO, this aspect of the argument regarding the credibility of homology-based assertion of function has been discredited.

In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on April17, 2001, in a talk by Senior Examiner James Martinell, it was emphasized that Applicant's assertion that his claimed protein "is a member of a family of proteins that already known based upon amino acid sequence homology" can be effective as an assertion of utility for the claimed sequence. According to Dr. Martinell, the proper question for the Examiner to ask, after searching the prior art for the claimed protein, is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins as is asserted?" The "two" [sic: three] possible answers that can be deduced from this prior art search are, according to Dr. Martinell:

- The search does not reveal any **evidence** that the family attribution made in the application is either **incorrect or may be incorrect**
- The protein either **more likely belongs to a family other than that asserted** in the application or **likely does not belong to the family asserted** in the application
- The search shows that the attribution is likely correct

(From handouts of Dr. Martinell's slides distributed April 17, 2001; emphasis added)

It is clear from the above that the tactic taken by the Examiner in asserting the very slight possibility that ANY minor sequence change might have a dramatic effect on the function of the protein has been abandoned by the USPTO as a credible basis for a rejection under either the utility requirement of 35 U.S.C. § 101 or the enablement requirement of §112, first paragraph.

However, in any case, it is noted that the Office Action has failed to meet the above requirements now recognized by the USPTO. The Office Action has cited no evidence <u>particular to the claimed protein</u>, e.g., inconsistent findings deduced from a search, upon which to base any objection to the assignment of functional homology to the family of protease inhibitor proteins, in particular, to the family of inter-α-trypsin inhibitor heavy chains. Indeed, there is no such evidence.

Moreover, it must be remembered, as set forth in the USPTO's own M.P.E.P. § 2107, that in order to raise such doubt in the veracity of Applicants' assertion, the Office Action must establish either (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. The Office Action has accomplished neither of these minimum standards.

C. Responses to Specific Arguments by Examiner

1. <u>Expression of GAPIP</u>

The Office Action disagrees that the use of GAPIP antibodies in toxicology testing constitutes a "real-world" use of GAPIP. The Office Action first asserts that "it is not clear that GAPIP even constitutes an 'expressed polypeptide' as asserted by Applicant" (Office Action, page 5).

The Office Action thus sets forth the novel theory that the central dogma of molecular biology (*i.e.*, DNA directs transcription of messenger RNA which in turn directs translation of protein) somehow does not apply to the discoveries of the present application. That is, the nucleotide sequence of SEQ ID NO:2 (which encodes the polypeptide of SEQ ID NO:1) was determined from a human

uterus cDNA library. That cDNA library in turn was made from messenger RNA isolated from human tissue. See the specification, for example, at pages 38-39. Thus, the nucleotide sequences of the present invention are expressed sequences. The Office Action purports that the existence of an expressed mRNA does not insure that the protein encoded by the mRNA will be translated and, hence, the claimed subject matter lacks patentable utility.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification, and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action does not cite any scientific evidence in support of the contrary position. While the Office Action mailed June 17, 2002 cited an example of inhibition of translation initiation, this example represents a comparatively unusual mechanism of gene regulation.

For example, a standard textbook in the field of molecular biology (*Molecular Cell Biology*) indicates that the *predominant* level of control of gene expression is at transcription. In discussing the complicated process of gene expression, Darnell et al. state,

> "gene control can occur at four levels: (1) transcription (either initiation or termination), (2) nuclear processing of primary transcripts, (3) cytoplasmic stabilization or destabilization of RNAs, and (4) mRNA translation. Enough examples have been analyzed to show that gene control at each of these levels occurs in eukaryotes, although not every gene is -- or can be -- controlled at all four levels.
>
> **Regulation of transcriptional initiation is by far the most widespread form of gene control in eukaryotes,** as it also is in prokaryotes. Such control results in the increased or decreased synthesis of primary RNA transcripts in response to some signal, leading to a change in the level of specific mRNAs and their translation products." (emphasis added).
>
> (*Molecular Cell Biology*, Darnell, J.E. et al., editors, Scientific American Books, Inc, 1990, 2nd Edition, page 397; Reference No. 4, enclosed).

Even in discussing posttranscriptional controls, Darnell et al. state that "[t]ranslational control of specific proteins has been proved in only a few cases" (Darnell, page 442), and that "differential

translational control of specific mRNAs is not common in eukaryotes" (Darnell, page 444). While Darnell et al. goes on to describe several examples of genes exhibiting posttranscriptional control, the fact that there are examples of a *few* genes that are regulated by posttranscriptional controls does not detract from the observation that the *preponderance* of genes are regulated at the level of transcription. This, therefore supports Applicants' assertion that mRNA levels are *usually* a good indicator of protein levels. No more is needed to demonstrate that one of skill in the art would believe Applicants' assertions were more likely than not to be correct.

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 expression correlates with the levels of SEQ ID NO:2 mRNA. Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels.

2. Toxicology testing is a specific, substantial and credible utility:

The Office Action asserts that the use of the claimed antibodies in toxicology testing does not constitute a "real-world" use for the claimed antibodies (Office Action, page 5). Applicants do not agree, because the Office Action has not considered all of the asserted and well-established utilities of the claimed antibodies. For example, the Examiner continues to view the utility of the claimed antibodies in toxicology testing as requiring knowledge of either their disease association or the biological function of the proteins to which they bind. The Examiner appears to view toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the protein bound by the claimed antibodies. The Examiner has refused to consider that the claimed antibodies are useful for measuring the toxicity of drug candidates which are targeted not to the protein bound by the claimed antibodies, but to **other** genes or proteins. This utility of the claimed antibodies does not require any knowledge of the biological function or disease association of the polypeptides they bind, and is a specific, substantial and credible utility.

The claimed antibodies can be used in just such a way to provide a practical, real world result. Monitoring the expression of the proteins bound by the claimed antibodies is a good method of testing the toxicology of drug candidates during the drug development process. This utility of the claimed antibodies is specific and substantial, and does not require any knowledge of the precise biological function or disease association of the polypeptides to which they bind.

Furthermore, the facts presented in the Rockett Declaration and its attached references demonstrate that the asserted utilities of the claimed antibodies in expression profiling and toxicology testing, far from applying ***regardless*** of the specific properties of the claimed antibodies, ***depend upon*** properties that allow them to identify specific proteins -- their binding specificities.

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of protein-antibody binding was well-established in the art far earlier than the development of antibody microarrays in the 1980s, and indeed is the well-established underpinning of many, perhaps most, immunoassay techniques over the past several decades.

3. Biological function is irrelevant to utility

The Office Action asserts that the exact biological role or function of GAPIP is required for the utility of the claimed antibodies to GAPIP in toxicology testing (Office Action, page 5). The Office Action is confusing, once again, function with use. These are not synonymous. Despite having different specific biological roles, protease inhibitors can indeed have many common uses, such as toxicology controls. In any event, it does not matter that there may be more than one use for protease inhibitors. The point for the purposes of the utility standard is that they are all indeed useful, which proves more than probable utility of the claimed invention.

4. Irrelevance of altered expression or disease association to utility in toxicology testing

The Office Action asserts that "in order to be useful for toxicology testing, there must be some indication of a condition where a putative toxin or agent would affect expression of GAPIP. However, there is no indication of any type of normal or abnormal expression of GAPIP in a 'real-world' context" (Office Action, page 5). This is irrelevant. Applicants need not demonstrate whether the polypeptides

bound by the claimed antibodies are associated with disease, only whether the claimed antibodies are useful. The claimed antibodies are useful whether or not the polypeptides they bind are associated with disease (for example, as controls in toxicology testing for drugs directed to other genes or proteins).

While expressly not conceding that an association with specific diseases is necessary to demonstrate the utility of antibodies to GAPIP, Applicants respectfully point out the ample evidence indicating an association between GAPIP and reproductive, developmental, neoplastic, and immunological disorders. In addition to being an inter-α-tyrpsin protease inhibitor, a member of a family whose members are known to regulate proteases involved in the complement cascade, blood clotting, and degradation and turnover of the extracellular matrix (specification, page 1, lines 17-20), Northern analysis shows that of the libraries in which GAPIP is expressed, at least 63% are associated with immortalized or cancerous tissues, and at least 26% are associated with the immune response (specification, page 15, lines 9-10). In addition, GAPIP is expressed in reproductive, gastrointestinal, nervous, and fetal tissues (specification, page 15, lines 10-11). Thus one of ordinary skill in the art would expect GAPIP to be associated with reproductive, developmental, neoplastic, and immunological disorders. Furthermore, as discussed above, the postfiling Himmelfarb paper confirms that the expression levels of ITIH5/GAPIP are correlated with neoplastic disorders such as breast cancer. The use of GAPIP in the treatment or diagnosis of breast cancer is disclosed in the specification at page 25 line 18 and page 35, line 4.

5. The Office Actions's reliance on *Brenner* v. *Manson* is misplaced

This is not a case in which biological function is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention is disclosed in the instant specification to be useful as a tool in a number of gene and protein expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function of the claimed antibodies or the polypeptides to which they bind is superfluous information for the purposes of establishing utility.

The uncontested fact that the claimed invention already has a disclosed use as a tool in then available technology (such as 2D PAGE maps or antibody arrays) distinguishes it from those few

claimed inventions found not to have utility. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Office Action's unsupported implication (Office Action, page 6) that one of those cases, *Brenner* v. *Manson*, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect.

Brenner concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the claimed antibody is one which binds to an expressed polypeptide that was disclosed to be useful in the instant specification for many known applications involving gene and protein expression analysis. Its utility is not a matter of guesswork. It is not a random antibody that might or might not be useful as a scientific tool. Unlike the steroid in *Brenner*, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions.

And, the utilities disclosed in the application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug for immune disorders.

Accordingly, in this case, biological function is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function. Given that the claimed

invention has disclosed and well-established utilities, the Applicants need not demonstrate utility by imputation.

In the end, the Office Action has failed to recognize that new technologies, such as those involving the use of 2D PAGE maps or antibody arrays, to conduct gene and protein expression analyses have made useful biological molecules that might not otherwise have been useful in the past. *See Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polypeptide (or an antibody that specifically binds to it) could be usefully employed without further research. It has created a need for new tools, such as the claimed antibodies, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and **real-world benefits** to the public by enabling faster, cheaper and safer drug discovery processes. The Patent Office is obliged, by law, to recognize this reality.

Enablement rejections under 35 U.S.C. §112, first paragraph

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Office Action, page 6). To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

In addition, claims 3, 5-6, 8, 11-12, 14-17, and 20-21 have been rejected as failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide sufficient guidance to enable the skilled artisan to make and use the claimed antibodies. In particular, the Office Action asserts that the specification does not provide sufficient guidance to make and use antibodies to a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:1, even when said naturally occurring sequence has protease inhibitor activity (Office Action, page 6). The Office Action does not dispute that the present application describes how to make an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or to an immunogenic fragment of SEQ ID NO:1.

The Office Action does not appear to dispute that conventional methods for making antibodies could be used to make antibodies which specifically bind to a polypeptide comprising a naturally

occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO:1. Instead, the Office Action asserts that the present disclosure is deficient because one of skill in the art would not be able to make the variant polypeptides of SEQ ID NO:1 *per se* and, hence, without the variant polypeptides, one would not be able to make antibodies which specifically bind to those variant polypeptides.

Applicants respectfully point out that claim 3 recites not only that the variant polypeptides are at least 90% identical to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of GAPIP) and SEQ ID NO:2 (the polynucleotide sequence encoding GAPIP), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application, for example, at page 12, line 12 to page 13, line 12; page 34, lines 2-8; page 34, lines 9-12; and Example VI at pages 44-45.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims. Conventional methods for making antibodies, such as those described at pages 26-28 of the specification, could then be used to make antibodies which specifically bind to the recited polypeptide variants.

Applicants further note that the claims are directed to <u>antibodies</u>, not to proteins; thus the functions of the proteins to which the claimed antibodies bind is not relevant. What matters is that the recited variants are sufficiently similar to SEQ ID NO:1 so as to retain the same structure to which the specific antibodies bind. Natural selection would tend to insure that the recited variants retain the same

structure as SEQ ID NO:1. As discussed by Brenner et al., as cited by the Office Action, proteins of closely related functions such as hemoglobin and myoglobin have very similar structures, even when their sequences are not similar (Office Action, page 4). Accordingly, proteins sharing the growth-associated protease inhibitor activity of SEQ ID NO:1 and having very high sequence similarity (at least 90%) to SEQ ID NO:1 would be even more likely to share conserved structures. For this reason, the antibodies which specifically bound the recited variants would not be highly variant from those specifically binding to SEQ ID NO:1.

Thus, regardless of the precise functional characteristics of the SEQ ID NO:1 variants, one can still make those polypeptide variants, and antibodies which specifically bind to the variants, using the disclosure provided by the present specification. The antibodies could then be used in, for example, diagnostic testing, drug discovery, expression profiling, etc. (See, e.g., the previously submitted Furness Declaration).

Furthermore, the Examiner's attention is also directed to the enclosed reference by Brenner et al. (*supra*). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

Claim 3 recites, *inter alia*, antibodies which specifically bind to "a polypeptide comprising . . . a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as growth-associated protease inhibitor heavy chain precursors and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "90% variants" recited by the present claims have a variation that is far less than that of all potential growth-associated protease inhibitor heavy chain precursors related to SEQ ID NO:1, i.e., those growth-associated protease inhibitor heavy chain precursors having as little as 40% identity over at least 70 residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional

activities of a growth-associated protease inhibitor heavy chain precursor.

> As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):
>
> The first paragraph of § 112 ***requires nothing more than objective enablement***. [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited antibodies which specifically bind to the recited variants of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established.

For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Written description rejection under 35 U.S.C. §112, first paragraph

Claims 3, 5, 6, 8, 11, 12, 14-17, and 20-21 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being based on a specification which provides an inadequate written description of what is claimed. The Office Action appears to urge that every single member of the claimed genus of polypeptides and the antibodies which bind them must be specifically disclosed by the Specification, otherwise an inadequate written description has been set forth. However, such a disclosure is not required for an adequate written description.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

The Office Action concurs that the specification provides adequate written description of an antibody which specifically binds the polypeptide of SEQ ID NO:1 or immunogenic fragments thereof; however, the Office Action asserts that the specification does not provide adequate written description of the antibodies to the recited variant polypeptides. The Office Action states that the specification "does not provide any description regarding the identification and protease inhibitor activity testing of other members of the "naturally occurring" polypeptide genus related to the nucleic acid encoding SEQ ID NO:1" (Office Action, page 8). To the contrary, given the information provided by SEQ ID NO:1 (the amino acid sequence of GAPIP) and SEQ ID NO:2 (the polynucleotide sequence encoding GAPIP), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of polynucleotides encoding the recited polypeptide variants could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application, for example, at page 12, line 12 to page 13, line 12; page 34, lines 2-8; page 34, lines 9-12; and Example VI at pages 44-45. Methods for assaying the protease inhibitor activity of the encoded variant polypeptides are described in the specification at page 47, lines 9-20. Conventional methods for making antibodies, such as those described at pages 26-28 of the specification, could then be used to

make antibodies which specifically bind to the recited polypeptide variants.

The Office Action further asserts that "there is not an adequate written description of antibodies to a protein comprising SEQ ID NO:1 or comprising fragments of SEQ ID NO:1" (Office Action, page 8). In order to further clarify the intended subject matter of the claimed invention, claim 3(c) has been amended herein to recite "an immunogenic fragment of SEQ ID NO:1." Thus the objection as it pertains to antibodies to a protein comprising fragments of SEQ ID NO:1 are moot. Regarding the recited sequences comprising SEQ ID NO:1, one of ordinary skill in the art would understand that SEQ ID NO:1 purified for use in antibody generation might also comprise heterologous protein and peptide moieties such as those described in the specification at page 23, lines 3-15. The antibodies encompassed by the claims, however, clearly are those which specifically bind to SEQ ID NO:1, not to these other moieties.

Applicants also respectfully point out that the claims are directed to antibodies, not proteins, and thus it is the properties of the antibodies, not the proteins they bind, which is relevant. The antibodies described by claim 3(a) and 3(c) both specifically bind to SEQ ID NO:1, a protein that is acknowledged to be described by the specification. Nor are the antibodies of claim 3(b) highly variant, given that they specifically bind to naturally occurring variants having at least 90% identity to SEQ ID NO:1. As discussed above, the genus of naturally occurring polypeptides having at least 90% identity to SEQ ID NO:1 is not highly variant. As discussed above, natural selection would tend to insure that the recited variants retain the same structure as SEQ ID NO:1, so that the antibodies which specifically bound the recited variants would not be highly variant from those specifically binding to SEQ ID NO:1.

For this reason, it would be clear to one of skill in the art that the specification and claims do define the structural features, or "common attributes of the genus" of the recited polypeptides that are relevant to the antibodies which bind them. In the case of the polypeptides recited in claim 3(c), the structural feature is clearly the immunogenic fragment of SEQ ID NO:1, since it is this fragment that determines the antibody binding specificity. Given that SEQ ID NO:1 is clearly disclosed in the specification, one of skill in the art would not have difficulty in recognizing fragments of SEQ ID NO:1. Additional description of immunogenic fragments is provided at, for example, page 48, lines 26-28, which disclose that appropriate epitopes include those near the C-terminus or in hydrophilic regions. For the polypeptides recited in claim 3(b), the structural feature is the 90% amino acid sequence identity

to SEQ ID NO:1. The fact that the recited variants are naturally occurring also in effect imposes a structural limitation, as these variants would have been selected by nature to retain the same overall structure as SEQ ID NO:1.

For at least the above reasons, withdrawal of the written description rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108.

Respectfully submitted,

INCYTE CORPORATION

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Attachments:

Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.13 with Exhibits A - Q.

1. Brenner et. al., "Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. 95:6073-78 (1998).
2. Hegyi, H., et al. "The relationship between protein structure and function: a comprehensive survey with application to the yeast genome," J. Mol. Biol. 288:147-164 (1999).
3. Himmelfarb, M. et al., "ITIH5, a novel member of the inter-α-trypsin inhibitor heavy chain family is downregulated in breast cancer," Cancer Lett. 204:69-77 (2004).
4. *Molecular Cell Biology*, Darnell, J.E. et al., editors, Scientific American Books, Inc, 1990, 2nd Edition, pages 397, 442-445.
5. Exhibit A: CLUSTALW sequence alignment of SEQ ID NO:1 and GI 30314037 (human ITIH5).